The Ohio State University Combined Consent to Participate in Research and HIPAA Research Authorization

Study Title: **A Phase I Study to Assess the Safety, Tolerability and Preliminary Efficacy of AAV2-BDNF [Adeno-Associated Virus (AAV)-based, Vector-Mediated Delivery of Human Brain Derived Neurotrophic Factor] in Subjects with Early Alzheimer's disease and Mild Cognitive Impairment**

Principal Investigator: **James Elder, MD**

Sponsor: **The Ohio State University**

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

Key Information About This Study

The following is a short summary to help you decide whether or not to be a part of this study. More detailed information is listed later in this form.

You are being asked to take part in this research study because you have Alzheimer's disease (AD) or Mild Cognitive Impairment (MCI). We are performing this study to test if a protein administered into the brain by gene therapy will slow or stop cell loss in the brains of people affected by AD and MCI. The protein may also help to activate cells in the brain.

Gene therapy means that we will use a naturally occurring human virus to make brain cells produce a protein called BDNF (Brain-Derived Neurotrophic Factor).

You will be given the AAV2-BDNF study drug into your brain during surgery by a brain surgeon. Your surgery will happen in the hospital and then you will be watched closely afterward until you are ready to go home. This may be one to two nights but it will be up to the study doctor to decide.

1. Why is this study being done?

The purpose of this study is to find out if the experimental study drug, AAV2-BDNF, is safe and well tolerated when given into the brain. This is a Phase I study that involves gene therapy. Phase I is the first and earliest stage of drug discovery for people. This means that the AAV2-BDNF you will be receiving has been studied by scientists using laboratory animals, but this study is the first time it is being given to people. We will perform this procedure in a total of 12 people with either Alzheimer's disease or with Mild Cognitive Impairment.

While AAV2-BDNF has not been given to people, another form of gene therapy called AAV2-NGF was given to 42 people with Alzheimer's disease. Of the 42 people, one died as a result of bleeding into the brain during the procedure. Another person had bleeding into the brain that they recovered from. These two patients were among the first 8 people treated, and the next 34 people treated did not have complications related to gene therapy.

What is Gene Transfer?

Gene transfer is a medical technique being studied in a number of diseases such as cancer, Parkinson's disease, and cystic fibrosis. Three gene transfer products have been approved by the Food and Drug Administration (FDA) and are on the market in the US for the treatment of 1) cancer, 2) a type of weakness caused by a gene mutation, and 3) one type of blindness caused by a gene mutation. All other gene transfer studies today are experimental.

The gene transfer part of this study involves AAV2-BDNF.

What is AAV2-BDNF?

AAV2-BDNF is a virus that holds the information (gene) to tell brain cells to make a substance called Brain Derived Neurotrophic Factor, or BDNF. It is made by putting a kind of virus called adeno-associated virus (AAV) together with a gene called the "BDNF gene". The goal is that it may make Alzheimer's disease better, stop it from

getting worse, or slow its progress. AAV viruses do not seem to cause people to get sick. The virus has been changed in the laboratory so that it only carries the gene for BDNF to the right place in the brain without multiplying and making you sick.

It is not known what the effect of AAV2-BDNF will be and there is no known benefit to it. This study is an experiment to see if AAV2-BDNF is safe to give to people. When given to the brains of animals, BDNF improves the survival of cells in the brain and improves their function. The purpose of this study is to determine whether we will also see these kinds of benefits in people with Alzheimer's disease and Mild Cognitive Impairment.

2. How many people will take part in this study?

12 people will receive AAV2-BDNF in this study.

3. What will happen if I take part in this study?

Screening Visit

A screening visit will be done to make sure that you are eligible to participate in the study. This visit may take place over multiple days. At the screening visit, the following will occur:

- **Physical exam:** You will have a physical exam, similar to those done for regular medical care.
- **Medical history:** The study team will collect your medical history, including information about your AD and MCI.
- **Neurological exam:** You will have a standard neurological exam including testing of strength, sensation and reflexes.
- **MRI:** You will have a brain Magnetic Resonance Imaging (MRI) exam. For the MRI exam, you will be asked to remove any metal objects and to lie down flat on your back on a narrow bed. The bed will then be moved into the MRI's imaging tunnel.
- **Neurological and cognitive assessments:** You will undergo some testing to assess your cognitive and neurological function as it relates to your AD or MCI.
- **Blood draw:** You will be asked to give a blood sample for laboratory tests. About 4 teaspoons of blood will be drawn by inserting a needle into a vein in your arm.
- **Urinalysis**: You will be asked to provide a urine sample for testing.
- **Chest x-ray: :** A chest X-ray will be performed as screening assessment to ensure you are healthy enough to participate in the study.
- **Electroencephalogram (EEG):** You will have an EEG done. This is a test that measures your brain waves through electrodes that are placed on our scalp.
- **Electrocardiogram (ECG):** You will have an ECG. This is a test that measures your heart's electrical activity through electrodes that are placed on the skin on your chest.

Baseline Visit

This visit may take a full day or may take place over two days.

- **Physical exam:** You will have a physical exam, similar to those done for regular medical care.
- **Neurological exam:** You will undergo a standard neurological exam including testing of strength, sensation and reflexes.
- **Lumbar puncture:** You will be asked to lay on your side and a needle will be inserted into your back to take a small sample of spinal fluid.
- **Blood draw:** You will be asked to give a blood sample for laboratory tests. About 4 teaspoons of blood will be drawn by inserting a needle into a vein in your arm.
- **Urinalysis:** You will be asked to provide a urine sample for testing.
- **FDG PET scan:** A FDG PET scan will be completed. An approved brain imaging chemical called fludeoxyglucose (FDG) will be injected into a vein in your arm. Then, a (positron emission tomography [PET]) brain scan will be performed. This will take approximately 60-90 minutes.
- **Amyloid and Tau PET scan:** Amyloid and Tau PET scans will be completed. These scans are to look at the buildup of proteins that are prime suspects in damaging and killing nerve cells in Alzheimer's. This will take approximately 60-90 minutes.
- **Neurological and cognitive assessments:** You will undergo some testing to assess your cognitive and neurological function as it relates to your AD or MCI.

Pre-operative visit

This visit will include a visit with the treating neurosurgeon and the anesthesiology team. This visit may include:

- **Physical exam:** You will have a physical exam, similar to those done for regular medical care.
- **Neurological exam:** You will undergo a standard neurological exam including testing of strength, sensation and reflexes.
- **Blood draw:** You will be asked to give a blood sample for laboratory tests. About 4 teaspoons of blood will be drawn by inserting a needle into a vein in your arm.
- **Urinalysis:** You will be asked to provide a urine sample for testing.
- **MRI:** You will have a brain MRI exam. For the MRI exam, you will be asked to remove any metal objects and to lie down flat on your back on a narrow bed which will then be moved into the MRI's imaging tunnel.

Surgical visit

You will be in the hospital for approximately 1-2 nights for the surgery to place the AAV2-BDNF in your brain. You will have brain surgery to make an opening in your skull so that the study drug, AAV2-BDNF, can be given into the brain during the procedure. After the surgery, if your condition is stable, you will be discharged from the hospital.

You will be admitted to the hospital on the morning of the surgery to inject AAV2-BDNF into your brain.

Before you are given the AAV2-BDNF you will be checked again to be sure that it is still safe for you to have the procedure and be given the study drug. The check-up will include checking your heart rate, blood pressure, breathing rate, and temperature. You will also be given a neurological (nervous system) examination to check your nervous system function, reflexes, and muscle strength. You will have a magnetic resonance image (MRI) scan. You will need to tell the study doctor about any new medications you may be taking, including vitamins, herbs, and supplements. Your companion may also be asked questions about you.

Samples of your blood will be collected again for testing including general blood cell count (CBC) and tests that look at your immunity and general state of health. Approximately 5 ¼ teaspoons will be needed to do this testing.

How will the AAV2-BDNF be given into my brain?

Depending on when you are enrolled into the study, you may receive a lower or higher dose than other participants. Additionally, some participants may receive injections on one side of the brain and other participants may receive injections on both sides of the brain.

You will be given general anesthesia to put you into a sleep-like state for the surgery. The surgery is called stereotaxic surgery because of the way all the areas of the brain are seen using the MRI pictures and the use of a special head frame explained below. You will receive anesthesia before the surgery so that you will not move or feel any pain during the surgery. This surgery will involve using a frame that is connected temporarily to your skull or scalp. The frame will hold the needle and tubing for injecting AAV2-BDNF very still and in the right position to give the AAV2-BDNF to the correct area of the brain where scientists think Alzheimer's disease may begin. This makes it possible to put the study drug in exactly the right place in the brain. AAV2-BDNF will be administered during the period that you are asleep, and while you are in a MRI scanner in the operating room, or in a special room attached to the MRI facility.

During part of the MRI, a needle will be placed into your vein (intravenous line or "IV") and dye will be injected. This dye helps to give a better picture of the brain and it will help the study doctor locate the exact place to put the AAV2-BDNF in the brain.

One or two small incisions (cuts) may be made at the top of the head and small holes called burr holes will be made into the skull. A very small amount of AAV2-BDNF (about 2 teaspoons) will be slowly injected into the area of the brain where Alzheimer's disease usually starts, the "entorhinal cortex." The injection of AAV2-BDNF into the brain is experimental and will take about 3 hours. You will be in the operating room for a total of approximately 6-8 hours including the injection time and set up time.

Following surgery, you will be monitored in the Neurosurgical Intensive Care Unit (ICU) as long as needed. We anticipate that in most cases this will be for about 1 day. You will then

either be moved to the regular Neurosurgery unit (a regular hospital room), or you may be discharged. At around 12 hours after the surgery, about 2 ¼ teaspoons of blood will be taken for testing. Around 24 hours after the surgery, approximately 5 teaspoons blood will be taken for testing. When you have recovered and your doctor feels you are stable enough to leave the hospital, you will be discharged.

Day 1

On the first day after surgery, the following will take place:

- **Physical exam:** You will have a physical exam, similar to those done for regular medical care.
- **Neurological exam:** You will undergo a standard neurological exam including testing of strength, sensation and reflexes.
- **Blood draw:** You will be asked to give a blood sample for laboratory tests. About 4 teaspoons of blood will be drawn by inserting a needle into a vein in your arm.
- **Urinalysis:** You may be asked to provide a urine sample for testing.

2 Weeks Post Treatment

- Physical exam
- Neurological exam
- **Blood draw:** You will be asked to give a blood sample for laboratory tests. About 4 teaspoons of blood will be drawn by inserting a needle into a vein in your arm.
- **Urinalysis:** You will be asked to provide a urine sample for testing.
- **MRI:** You will have a brain MRI exam. For the MRI exam, you will be asked to remove any metal objects and to lie down flat on your back on a narrow bed which will then be moved into the MRI's imaging tunnel.

1 Month Post-Treatment

- Physical exam
- Neurological exam
- **Neurological and cognitive assessments:** You will undergo some testing to assess your cognitive and neurological function as it relates to your AD or MCI.
- **Electroencephalogram (EEG):** You will have an EEG done. This is a test that measures your brain waves through electrodes that are placed on our scalp.

3 Months Post-Treatment

- Physical exam
- Neurological exam
- **Blood draw:** You will be asked to give a blood sample for laboratory tests. About 5 teaspoons of blood will be drawn by inserting a needle into a vein in your arm.
- **Urinalysis:** You will be asked to provide a urine sample for testing.
- **Neurological and cognitive assessments:** You will undergo some testing to assess your cognitive and neurological function as it relates to your AD or MCI.

- **Electroencephalogram (EEG):** You will have an EEG done. This is a test that measures your brain waves through electrodes that are placed on our scalp.

6 Months Post-Treatment

- Physical exam
- Neurological exam
- MRI
- **Blood draw:** You will be asked to give a blood sample for laboratory tests. About 5 teaspoons of blood will be drawn by inserting a needle into a vein in your arm.
- **Urinalysis:** You will be asked to provide a urine sample for testing.
- **Neurological and cognitive assessments:** You will undergo some testing to assess your cognitive and neurological function as it relates to your AD or MCI.
- **Electroencephalogram (EEG):** You will have an EEG done. This is a test that measures your brain waves through electrodes that are placed on our scalp.

9 Months Post-Treatment

- Physical exam
- Neurological exam
- **Neurological and cognitive assessments:** You will undergo some testing to assess your cognitive and neurological function as it relates to your AD or MCI.

12 Months Post-Treatment

- Physical exam
- Neurological exam
- **MRI:** You will have a brain MRI exam. For the MRI exam, you will be asked to remove any metal objects and to lie down flat on your back on a narrow bed which will then be moved into the MRI's imaging tunnel.
- **FDG PET scan:** You will have a FDG PET scan. A FDG PET scan is an approved brain imaging chemical called fludeoxyglucose (FDG) will be injected into a vein in your arm. Then, a (positron emission tomography [PET]) brain scan will be performed. This will take approximately 60-90 minutes.
- **Tau PET scan:** A Tau PET scan will be completed. This scan is to look at the buildup of proteins that are prime suspects in damaging and killing nerve cells in Alzheimer's. This will take approximately 60-90 minutes.
- **Lumbar puncture:** You will be asked to lay on your side and a needle will be inserted into your back to take a small sample of spinal fluid.
- **Blood draw:** You will be asked to give a blood sample for laboratory tests. About 5 teaspoons of blood will be drawn by inserting a needle into a vein in your arm.
- **Urinalysis:** You will be asked to provide a urine sample for testing.
- **Electroencephalogram (EEG):** You will have an EEG done. This is a test that measures your brain waves through electrodes that are placed on our scalp.
- **Neurological and cognitive assessments:** You will undergo some testing to assess your cognitive and neurological function as it relates to your AD or MCI.

18 Months Post-Treatment

- Physical exam
- Neurological exam
- **Electroencephalogram (EEG):** You will have an EEG done. This is a test that measures your brain waves through electrodes that are placed on our scalp.
- **Neurological and cognitive assessments:** You will undergo some testing to assess your cognitive and neurological function as it relates to your AD or MCI.

24 Months Post-Treatment

- Physical exam
- Neurological exam
- **MRI:** You will have a brain MRI exam. For the MRI exam, you will be asked to remove any metal objects and to lie down flat on your back on a narrow bed which will then be moved into the MRI's imaging tunnel.
- **FDG PET scan:** If a FDG PET scan is completed, an approved brain imaging chemical called fludeoxyglucose (FDG) will be injected into a vein in your arm. Then, a (positron emission tomography [PET]) brain scan will be performed. This will take approximately 60-90 minutes.
- **Tau PET scan:** A Tau PET scan will be completed. This scan is to look at the buildup of proteins that are prime suspects in damaging and killing nerve cells in Alzheimer's. This will take approximately 60-90 minutes.
- **Lumbar puncture:** You will be asked to lay on your side and a needle will be inserted into your back to take a small sample of spinal fluid.
- **Blood draw:** You will be asked to give a blood sample for laboratory tests. About 5 teaspoons of blood will be drawn by inserting a needle into a vein in your arm.
- **Urinalysis:** You will be asked to provide a urine sample for testing.
- **Electroencephalogram (EEG):** You will have an EEG done. This is a test that measures your brain waves through electrodes that are placed on our scalp.
- **Neurological and cognitive assessments:** You will undergo some testing to assess your cognitive and neurological function as it relates to your AD or MCI.

4. How long will I be in the study?

The total time for the active study is up to 1-2 months before getting AAV2-BDNF and then 24 months (2 years) after the study drug is given. Then you will be seen yearly.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are

otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

Blood Draws

There may be some temporary pain, bruising, bleeding, or, rarely, infection at the site where blood samples are drawn from your arm. Although rare, some individuals may become faint during blood drawing procedures. These complications are rarely severe.

MRI Scan

MRI is a painless imaging test and is very safe for most people You might experience some discomfort since you must lie flat in a long plastic cylinder for about 30-45 minutes. Some people also feel nervous due to fear of being in closed spaces. You will be closely watched at all times and can be helped if needed by the hospital staff during the scan. You may be moved out of the machine at your request. If you get very nervous, you may be given calming medication to make you feel better. Earplugs are available to decrease the clanking noise that is made by the machine. Pillows will be placed under your knees to make you comfortable and you will be covered with a sheet or blanket to keep you warm, if needed.

A small percentage of people may develop brief reactions to the dye used in MRI testing. These reactions might include including nausea, headaches, hot flashes, and heart palpitations (heart skipping a beat). A small group of people may also be allergic to the dye and may develop a rash, itching, hives, breathing difficulties, and, in extreme cases, death. You will be closely monitored throughout the procedure and if an allergic reaction develops, you will be treated promptly. It is also possible for the dye to cause kidney damage or, very rarely, to cause a chronic body-wide disease called nephrogenic system fibrosis, which can affect multiple organs. Nephrogenic System Fibrosis is a rare condition that occurs in people with severe kidney failure who receive gadolinium. This disease causes fibrosis (the formation of too much connective tissue in the skin and internal organs). The symptoms include:

- Swelling and tightening of the skin
- Reddened or darkened patches on the skin
- Thickening and hardening of the skin, typically on the arms and legs and sometimes on the body, but almost never on the face or head
- Skin that may feel "woody" and develop an orange-peel appearance
- Burning, itching or severe sharp pains in areas of involvement

- Skin thickening that inhibits movement, resulting in loss of joint flexibility

Rarely, blisters or ulcers

You should notify the study team or MRI staff if:

- You are allergic to gadolinium
- You have kidney problems

Because a strong magnet is used for the test, there are some people who may be injured if they have an MRI. This includes people who have heart pacemakers, other pacemaker wires in the heart, infusion pumps that must be connected at all times, surgical and/or brain aneurysm clips, shrapnel, metal prosthesis like pins in the legs or rods in the spine, and other things inside the body with potential magnetic properties, like metal pieces in the eyes (e.g., former welders).

You need to tell the study doctor if you worry that you may have any of these conditions before signing this consent form or having an MRI in order to be sure it is safe to do so. Anyone with one of the above conditions will not be allowed to enter the study.

Lumbar puncture

A safe way to access the Cerebral Spinal Fluid (CSF) is through the low back far away from your spinal cord by a lumbar puncture (spinal tap). A spot on your back will be numbed using a local anesthetic injection and you will be asked to lay on your side. This will be done at the bedside under typical sterile conditions. X-ray guidance may be used. You will be awake during this procedure You may experience a brief pain or a tingling sensation in your legs during the procedure. If this happens, please let the doctor know immediately and the needle may be adjusted. You may experience discomfort from lying still and your low back may be sore after the numbing medication wears off.

There is a small risk of bleeding and infection. About a third of people will experience a headache after a lumbar puncture that worsens when sitting or standing. This will often improve on its own, but some people require drinking extra fluids, caffeinated beverages, and/or mild pain relievers. Headaches lasting longer than 7 days develop in 1 in 50 to 200 lumbar punctures, though most resolve gradually by 2 weeks.

Rarely, some people with a prolonged headache will require a procedure called a blood patch. A blood patch uses a small amount of blood removed from a vein in your arm and then injecting it into the area of your back where the lumbar puncture was performed to seal off any possible leaks of CSF that may be causing the prolonged headache.

Surgery for AAV2-BDNF delivery

The surgical risks from the procedure you will have to inject the study drug will depend on your condition before the surgery.

There are lesser risks that are more likely to occur including bleeding, bruising, skin infection, and pain at the incision site.

The rare but more serious risks from brain surgery are mostly related to the surgical procedure. These risks may include hemorrhage (bleeding in the brain), stroke, permanent neurological injury, problems related to the anesthesia, an infection within the skull or brain, paralysis (being unable to move part of all of the body), infection, coma, and death. Worsening of nervous system function can occur, such as weakness in the arm or leg, loss of feeling over parts of your body, partial or complete loss of function such as speech and understanding, and worsening of other nervous system functions related to intellectual capacity, such as memory. The risk of stroke or significant bleeding within the brain most commonly happens during the procedure or within the following 24 hours. If a significant bleed or stroke occurs, it may produce neurological problems like weakness, difficulty with speech and walking, or death.

Additional risks include allergic or other reactions (such as upset stomach, headache, or fatigue) to medications given as part of the surgical anesthesia.

Likely:

- Tenderness at incision site(s)
- Headache
- Facial swelling
- Scalp numbness near the incision(s)

Less Likely

- Nasal congestion (stuffy nose)
- Nausea
- Infection of surgical wounds
- Bleeding or edema (swelling) in the brain along the injection track causing only minimal or temporary symptoms such as difficulty swallowing, hoarseness, or weakness in the arms or legs.

Rare but serious

- Skull fracture (broken skull bone) caused by keeping the skull in place during the surgical procedure. This is very rare and happens more often in children than adults. These fractures typically heal over time without any treatment, although in rare cases surgical repair may be needed.
- Stroke is brain cell injury and death as a result of not enough blood delivered to the brain. It can occur spontaneously or as a result of passage of the infusion catheter into the brain. It may or may not have bleeding associated with it. Neurological problems from stroke are related to the area of the brain that is

affected. Problems from stroke range from not causing any specific neurological problems to permanent neurological injury or death.

- Cerebral hemorrhage (bleeding in the brain) can occur spontaneously, in association with passage of the brain infusion catheter, or in associated with a stroke (blockage of a brain blood vessel that subsequently bleeds). These hemorrhages can either cause no neurological problems and resolve on their own or may require surgery or other medical treatments to control the bleeding. Problems can range from none requiring treatment to permanent neurological deficits or death despite all treatment, including additional surgery.
- Blood clots in the legs or lungs. This is a rare event, but can occur with any surgery, and can require that you take blood thinners for an extended period of time (months). It can result in serious heart or lung issues, and even death.
- Death, usually in association with known complications, but rarely due to unknown reasons.

The risks of these procedures will be discussed with you by the study doctor and you may discuss them with your personal doctor before deciding to volunteer for this study.

Risks of the virus (AAV) and protein (gene for Brain Derived Neurotrophic Factor) combined as AAV2-BDNF

Adeno-associated virus (AAV) has not been known to cause disease in people. The potential risks of AAV2-BDNF include, but are not limited to:

- Allergic reaction to the virus causing symptoms ranging from itching and hives to severe cases involving difficulty breathing
- Tinging sensations in the arms and legs, weight loss, and changes in brain cells
- Infection of the brain (encephalitis), which may cause high fevers, confusion, loss of consciousness, neurologic difficulties, seizures, and even death
- Worsening memory
- Seizures: Seizures did not occur in monkeys treated with a regular dose of gene therapy when injections into the brain were made in the right brain location. However, seizures occurred in 10-15% of monkeys when the treatment went to the wrong brain location. The study doctors are using MRI-guided injections in people to accurately deliver AAV2-BDNF to the right place and avoid seizures. Seizures developed in most animals that received much higher doses of AAV2-BDNF than planned for this study.

If you develop seizures, you will be given anti-seizure medications such as lamotrigine (Lamictal) or levetiracetam (Keppra). These medications are often, but not always, successful in stopping seizures in people with epilepsy. However, we do not know that these drugs will be effective if AAV2-BDNF causes seizures. There is a possibility that seizures might not be treatable, and this could worsen your dementia. It is also possible that seizures could result in your death if the seizures are

not stopped soon enough. You should be aware of the risk of developing seizures if you enter this study, and that seizures could worsen your dementia or cause your premature death.

There is a risk that you could develop a brain infection or other infection. The virus in this study has been changed to prevent the virus from multiplying but AAV2-BDNF has never been given to humans before this study so all risks and side effects cannot be known.

Brain infection is not an expected side effect of AAV2-BDNF. However, if you should get an infection of the brain, you will be treated with the standard medical therapy for this infection. This could require that you be hospitalized or stay longer in the hospital after surgery to receive care. You could also have an examination of your spinal fluid if a brain infection is suspected by your study doctor. If a sample of spinal fluid is needed, a small needle will be placed in the small of the back into the space around the spinal cord (lumbar puncture) and a sample of spinal fluid (about one teaspoon) will be removed. This can result in headaches and, in rare cases, worsening of nervous system functioning. This examination will only be done if brain infection is suspected.

A brain biopsy may be necessary in rare cases of infection. Brain biopsy can cause bleeding, infection, and possible worsening of nervous system function. The biopsy would only be done if a severe brain infection was confirmed.

Your doctor will discuss these procedures with you and/or your family if it becomes necessary to perform them.

You will need to avoid close contact with immunocompromised individuals, pregnant women, young children, and infants for two weeks after the surgical procedure.

Cancer

It is possible that AAV vectors cause cancer in cells that are exposed to AAV2-BDNF. In one animal study, mice were given AAV by injection into a vein and not directly into the brain and tumors grew months after the mice received AAV. Scientists do not know if the tumor growth was related to the use of AAV or because of the underlying disease in the mice. Other studies of AAV in animals have not shown that tumors develop and grow after AAV is given. There have been no reports of cancer in humans who have been given AAV gene transfer, and there were no cases of brain cancer in 34 Alzheimer's patients who received AAV2-NGF.

Radiation Risks

This research study involves exposure to radiation from a chest x-ray, 3 FDG PET scans, an Amyloid PET scan, and 3 Tau PET scans. This radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation that you will receive in this study is about 80.12mSv, and is approximately equivalent to a whole-body exposure of approximately 13years of exposure to natural background radiation. The use of radiation in this study has been reviewed by the Human Subjects Radiation Committee. This committee has approved this use as involving acceptable risk and that it is necessary to obtain the research information desired.

Neurological and Cognitive Assessments

Some of the neurological and cognitive assessments ask sensitive questions, such as regarding depression and suicidal thoughts. If you are struggling with thoughts and feelings of depression and suicide, a helpful resource is the suicide prevention hotline which can be reached by dialing **988**.

Confidentiality

It is possible that your confidential health information could be unintentionally disclosed. A number of safeguards are put in place to protect your confidentiality to prevent unintentional disclosure of your confidential information.

Unknown Risks

AAV2-BDNF is new and it is not possible to know or tell you all of the problems or side effects that may occur, including the possibility of unknown and possibly disabling effects or death.

New Findings

Any important new findings that develop during the study that may affect your willingness to continue in the research will be provided to you by the study doctor or staff.

7. What benefits can I expect from being in the study?

There is no known clinical benefit to you for taking part in this study. While it is possible that this experimental treatment may have some benefit, there may still be no beneficial effect on the course of your Alzheimer's disease or Mild Cognitive Impairment.

Because of your participation in this study, we may learn more about potential ways to treat Alzheimer's disease and Mild Cognitive Impairment. This information may benefit future patients with Alzheimer's disease and Mild Cognitive Impairment.

8. What other choices do I have if I do not take part in the study?

You are being offered the opportunity to participate in this study because you have Alzheimer's disease or Mild Cognitive Impairment.

Other therapy options have been explained to you, including:

- Medications you take by mouth (Aricept, Memantine, etc.)
- Usual standard-of-care treatment for Alzheimer's disease
- Non-participation in this study

There are no other standard treatments that have been shown to have significant effects in patients with your disease. A variety of experimental studies for the treatment of Alzheimer's disease are done in medical centers around the world, but the benefit of these is as yet unknown. In addition, you may decline any further treatment for your disease.

If you are asked to enroll in another study after you agree to be part of this one, you will need to tell the study doctor and your personal doctor before you participate in the other study.

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

9. What are the costs of taking part in this study?

There will be no cost to you if you participate in this research study. All study related medications, examinations, and medical treatment will be provided at no cost.

10. Will I be paid for taking part in this study?

You will be reimbursed for travel expenses such as airfare, and mileage if you have to travel more than 100 miles. Travel costs that will be reimbursed or directly covered include airfare, per-day meal costs, lodging (e.g. hotel), airfare, and vehicle rental. All travel costs will be covered following institutional guidelines for milage reimbursement, standard per-day meal costs, and lodging costs.

By law, payments to participants are considered taxable income.

11. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

12. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of research participants.

13. Will my de-identified information and bio-specimens be used or shared for future research?

Yes, they may be used or shared with other researchers without your additional informed consent.

14. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and

- Your insurance company (if charges are billed to insurance).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search the website at any time.

15. HIPAA AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

I. What information may be used and given to others?

- Past and present medical records;
- Research records;
- Records about phone calls made as part of this research;
- Records about your study visits;
- Information that includes personal identifiers, such as your name, or a number associated with you as an individual;
- Information gathered for this research about:
  Physical exams
  Laboratory, x-ray, and other test results
  The diagnosis and treatment of a mental health condition
- Records about any study drug you received

II. Who may use and give out information about you?

Researchers and study staff.

III. Who might get this information?

- The sponsor of this research. "Sponsor" means any persons or companies that are:
  - working for or with the sponsor; or
  - owned by the sponsor.
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information;
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office record;

IV. Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, and other federal and state entities;
- Governmental agencies in other countries;

- Governmental agencies to whom certain diseases (reportable diseases) must be reported; and
- The Ohio State University units involved in managing and approving the research study including the Office of Research and the Office of Responsible Research Practices.

V. Why will this information be used and/or given to others?

- To do the research;
- To study the results; and
- To make sure that the research was done right.

VI. When will my permission end?

There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

VII. May I withdraw or revoke (cancel) my permission?

Yes. Your authorization will be good for the time period indicated above unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the researchers. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

VIII. What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study and receive research-related treatment. However, if you are being treated as a patient here, you will still be able to receive care.

IX. Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

X. May I review or copy my information?

Signing this authorization also means that you may not be able to see or copy your study-related information until the study is completed.

16. Who can answer my questions about the study?

For questions, concerns, or complaints about the study, or if you feel you have been harmed as a result of study participation, you may contact **Dr. Brad Elder at 614-366-8327.**

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact

HIPAA Privacy Officer
Suite E2140
600 Ackerman Road
Columbus, OH 43202
614-293-4477

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact **Dr. Brad Elder at 614-366-8327.**

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this combined consent and HIPAA research authorization form**.**

Printed name of participant	**Signature of participant**
	AM/PM
	Date and time
Printed name of person authorized to consent for participant (when applicable)	**Signature of person authorized to consent for participant (when applicable)**
Relationship to the participant	**AM/PM** **Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time